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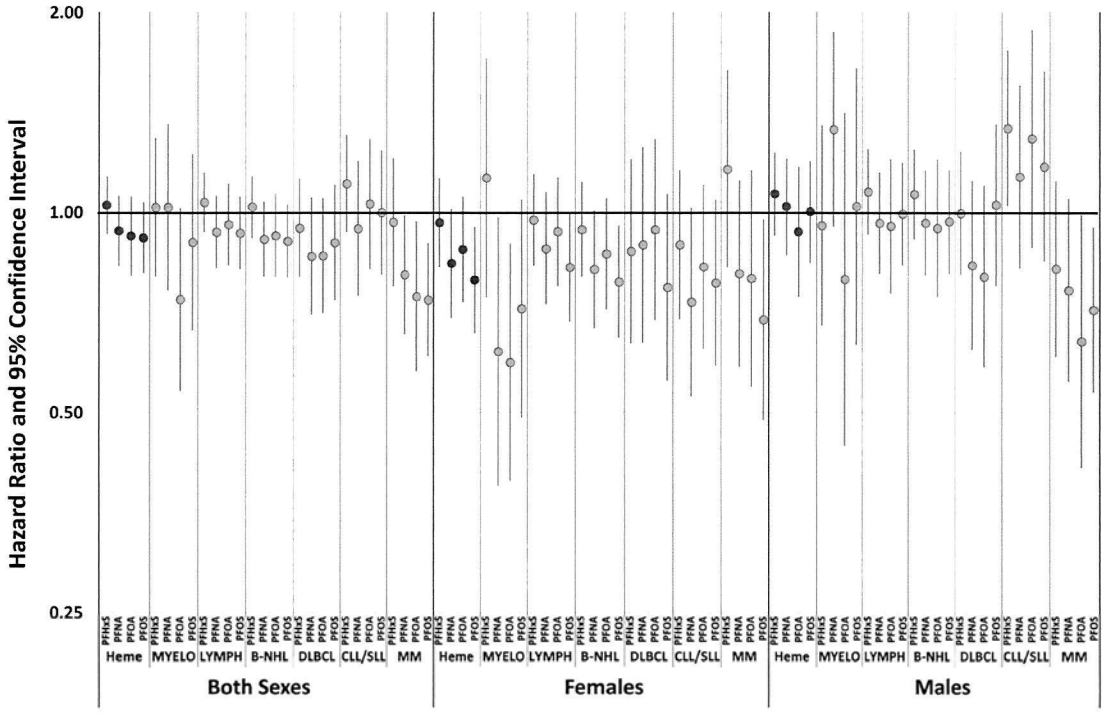

Figure 3. Hazard ratios and 95% confidence intervals for overall hematologic malignancies (dark circles) and histologic subtypes (light circles) for hematologic subtypes per doubling of PFAS concentrations (using $\log_2$-transformed measures) by sex and type of PFAS, case–cohort study of association between PFAS and selected cancers among participants in the Cancer Prevention II LifeLink cohort, 1998–2015. All models had separate baseline hazards by sex or were restricted to one sex. The primary models controlled for year of serum sample collection (single-year categories), age at serum collection (<60, 60–64, 65–69, 70–74, 75–79, ≥80 y), race (non-Hispanic White, other), education (high school graduate or less, vocational/trade school or some college, college graduate, graduate school), smoking status (current smoker, former smoker, ever smoked but unknown if current or former, never smoked), and alcohol consumption (nondrinker, <1 drink/wk, 1–6 drinks/wk, 1 drink/d, ≥2 drinks/d). The overall number of cancers (both sexes) included in the models were as follows: Heme, 626; MYELO, 80; LYMPH, 540; B-NHL, 483; DLBCL, 123; CLL/SLL, 140; MM, 99. See Tables S9 and S10 for numerical data. Note: B-NHL, B-cell non-Hodgkin leukemia/lymphoma; CLL/SLL, chronic lymphocytic leukemia/small lymphocytic lymphoma/mantle cell lymphoma; DLBCL, diffuse large B-cell lymphoma; Heme, hematologic malignancies; LYMPH, lymphoid malignancies; MM, multiple myeloma; MYELO, myeloid malignancies; PFAS, per- and polyfluoroalkyl substances; PFHxS, perfluorohexane sulfonic acid; PFNA, perfluorononanoic acid; PFOA, perfluorooctanoic acid; PFOS, perfluorooctane sulfonate.

skin cancer. At the time of the baseline serum collection in 1998–2001, 79% of those included in our subcohort were ≥65 y of age. PFAS exposure has been ongoing in the United States for many years. PFAS production started in the 1940s, and global emissions of perfluoroalkyl carboxylic acids (such as PFOA and PFNA) steadily increased until approximately 2000–2002.[23,102] PFAS concentrations in human serum in the U. S. NHANES survey were first measured during the 1999–2000 NHANES cycle, and PFOS, PFOA, PFHxS, and FOSA were detected in all samples.[19] Therefore, CPS-II LifeLink Cohort participants almost certainly were exposed to several PFAS for many years before serum collection in 1998–2001, and the study is left-truncated. In the presence of varying susceptibility to the effect of exposure on disease, left truncation can lead to bias in measures of the effect of an exposure on disease.[103–106] Bias resulting from left truncation can occur because those who are most susceptible to the effect of exposure on disease are lost over time from the population that remains at risk for the outcome, leaving a population that is less susceptible to the effects of the exposure on disease.[103,104] This is a type of selection bias,[106] the magnitude of which can increase with increasing time between the start of exposure and study enrollment[103]; it can lead to underestimation of positive associations and can result in an exposure that has a harmful effect appearing to have a protective effect.[105–107] Ongoing exposure prior to enrollment also complicates control for some variables, such as BMI, which might confound some PFAS associations but might also be caused by PFAS exposure and therefore potentially on the causal pathway between PFAS exposure and the outcome.[104] Some left-truncation is unavoidable in U.S. epidemiological studies of PFAS and cancer outside historical settings. However, for this study, the effect of left truncation might have been particularly pronounced, because observation for many participants started at an age that is older than the median age at diagnosis for some of the cancers considered, especially for kidney and breast cancers.[108] Left-truncation could have led to underestimation of some HRs and could explain some of our observed negative associations but is unlikely to have led to overestimation of HRs.

Another study limitation is that that PFAS serum concentrations are available for only one point in time, and the degree to which this measurement would adequately represent a person's PFAS exposure history is uncertain. However, there are several reasons to expect that the serum concentrations would adequately reflect a person's longer-term exposures. Our analysis can be considered as essentially addressing the question of whether people with higher PFAS serum concentrations have a higher cancer incidence than those with lower PFAS concentrations, with the assumption being that a person's PFAS exposure ranking in relation to others with similar covariates (e.g., age, sex) and with serum drawn around the same time remains relatively stable over time, even if absolute concentrations change. This assumption is likely reasonable, given *a*) the long half-lives of several PFAS,[8,25,26] and *b*) the facts that PFAS have been used for long

periods of time,[102] are persistent in the environment,[102] and have only relatively recently come to attention in drinking water.[10] One study that examined within-individual changes in serum PFAS concentrations over time in a population with PFAS exposure at general-population levels found that the ranking of individuals' serum concentrations remained relatively stable, even though absolute concentrations changed over time.[109] Our PFAS serum concentrations were also only for the linear isomers of the PFAS considered, which might limit comparability of our findings to those of other studies of PFAS and cancer.

It is also important to note that concentrations of the various PFAS were correlated, so HRs for one type of PFAS should be interpreted as possibly also representing the effects of other correlated PFAS. The number of cancer cases in our study did not allow for more complex models controlling for other PFAS. Nevertheless, there is no guarantee that models controlling for other PFAS would be less biased than single-PFAS models. If unmeasured exposures (e.g., diet) confound the association between the outcome and one type of PFAS, but not another type of PFAS, including both types of PFAS in the model could amplify, not decrease, bias.[110] In addition, associations could be confounded by other correlated but unmeasured PFAS. Nevertheless, the inability to control for other PFAS limits our ability to confidently conclude that associations observed for kidney cancer among women and CLL/SLL among men are solely attributable to specific PFAS. Consideration of PFAS mixtures is an important area for exploration in future studies of PFAS and cancer.

Although this study includes more cases of the cancers considered than many previous studies, the number of cases for some of the cancer subtypes considered might have been small relative to the number of variables in our models, with some variables involving multiple parameters. Some have suggested that having fewer than 10 cases per model parameter can lead to bias,[111,112] but others have suggested that bias is unlikely with case counts as low as five cases per parameter.[113] Models for bladder, breast, prostate, and the larger hematologic malignancy subgroups had an ample number of cases relative to the number of parameters, but models for kidney cancer, pancreatic cancer and smaller hematologic subtypes had a fewer cases per parameter (Table S11). Model results should be interpreted considering this limitation. The fact that models with collapsed categories of some control variables gave similar conclusions provides some reassurance that low case numbers might not have seriously biased the primary model results. Finally, our results should be interpreted with consideration of the fact that there are multiple comparisons, and some observed associations could be due to chance or unknown sources of bias.

In conclusion, this study provides important information supporting the previously observed association between PFOA and kidney cancer, particularly among women, at general population-level PFAS exposures. It also contributes to evidence relating to PFAS exposure and specific types of hematologic malignancies, which have been less commonly studied, and not previously studied in a population with general-population-level PFAS exposures. It suggests a possible association between PFAS exposure and CLL/SLL among men that could be followed-up in future studies. Study findings also indicate that consideration of histologic subtypes might be important in future studies of PFAS and cancer, especially for hematologic malignancies.

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Supplemental Material

Case–Cohort Study of the Association between PFAS and Selected Cancers among Participants in the American Cancer Society's Cancer Prevention Study II LifeLink Cohort

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Table S1. Definitions used for cancer histologic subtypes using International Classification of Disease for Oncology (ICD-O) histology codes

Cancer site and histologic subtypes	**ICD-O codes**
Kidney-all	All
Renal cell carcinoma/adenocarcinoma (RCC)	8010, 8260, 8310, 8312, 8317, 8318, 8323
Bladder -all	All
Transitional cell carcinoma of the bladder (TCC-B)	8120, 8122, 8130
Transitional cell carcinoma of the bladder or kidney (TCC-BK)	8120, 8122, 8130
Breast (female only)	All
Prostate (male only)	All
Pancreas- all	All
Non-islet cell carcinoma/neuroendocrine tumors	Excluding 8150, 8246
Hematopoietic (lymphoma, leukemia or myeloma)- (Heme)	All
Myeloid malignancies (MYELO)	9840, 9860, 9861, 9863, 9867, 9871, 9872, 9873, 9874, 9875, 9876, 9891, 9895, 9920, 9945
Lymphoid malignancies (LYMPH)	9590, 9591, 9596, 9650, 9652, 9663, 9670, 9671, 9673, 9675, 9680, 9684, 9687, 9689, 9690, 9691, 9695, 9698, 9699, 9700, 9701, 9702, 9705, 9709, 9714, 9718, 9728, 9729, 9732, 9823, 9827, 9831, 9834, 9835, 9940
Non-Hodgkin Leukemia/Lymphoma (NHL)[b]	9591, 9670, 9671, 9673, 9675, 9680, 9684, 9687, 9689, 9690, 9691, 9695, 9698, 9699, 9700, 9701, 9702, 9705, 9709, 9714, 9718, 9728, 9729, 9732, 9823, 9827, 9831, 9834, 9835, 9940
NHL without Multiple Myeloma (NHL without MM)	9591, 9670, 9671, 9673, 9675, 9680, 9684, 9687, 9689, 9690, 9691, 9695, 9698, 9699, 9700, 9701, 9702, 9705, 9709, 9714, 9718, 9728, 9729, 9823, 9827, 9831, 9834, 9835, 9940
B-cell NHL (B-NHL)	9670, 9671, 9673, 9680, 9687, 9689, 9690, 9691, 9695, 9698, 9699, 9728, 9732, 9823, 9940
B-cell NHL without Multiple Myeloma (B-NHL without MM)	9670, 9671, 9673, 9680, 9687, 9689, 9690, 9691, 9695, 9698, 9699, 9728, 9823, 9940
Diffuse Large B-cell Lymphoma (DLBCL)	9680
Chronic lymphocytic leukemia/Small lymphocytic lymphoma/Mantle cell lymphoma (CLL/SLL)	9670, 9673, 9823
Multiple Myeloma (MM)	9732

Table S2. Comparison of characteristics of study participants for the Overall CPS-II[a] LifeLink cohort (n=39,371), the CPS-II LifeLink Cohort Meeting Case-cohort Study Inclusion Criteria[b] (n=29,985), and participants selected for the sub-cohort[c] (n=1000 selected, 999 with PFAS[a] serum measurements[d]), Case-cohort study of association between PFAS and selected cancers among participants in the Cancer Prevention II LifeLink cohort, 1998-2015

	CPS-II[a] LifeLink	CPS-II[a] LifeLink Cohort Meeting Study Inclusion Criteria[b]	Participants selected for the sub-cohort[c]	Participants in the sub-cohort with PFAS measurements[d]
Overall number	39,371	29,985	1000	999
% women	56%	56%	50%	49.95%
% Non-Hispanic white race	98%	98%	98.2%	98.2%
% college graduate	46%	46%	44.8%	44.8%
% current cigarette smokers in 1997	4%	4%	3.9%	3.9%
Age range at blood collection (years)	47-94	49-94	54-86	54-86
Median age at blood collection (years)	70	69	69	69
Women-n	21,963	16,727	500	499
% Non-Hispanic white race	98%	98%	99.0%	99.0%
% college graduate	38%	37%	37%	37.07%
% current cigarette smokers in 1997	4%	4%	4.2%	4.2%
Age range at blood collection (years)	47-88	49-88	54-82	54-82
Median age at blood collection (years)	69	68	68	68
Men-n	17,408	13,258	500	500
% Non-Hispanic white race	98%	98%	97.4%	97.4%
% college graduate	57%	57%	52.6%	52.6%
% current cigarette smokers in 1997	4%	4%	3.6%	3.6%
Age range at blood collection (years)	51-94	51-94	57-86	57-86
Median age at blood collection (years)	71	70	70	70

[a] CPS-II=Cancer Prevention Study II, PFAS=per- and polyfluoroalkyl substances

[b] Study inclusion criteria for the sub-cohort included the following:

1) no previous cancer diagnosis (other than non-melanoma skin cancer) at the time of blood sample collection (1998-2001)
2) at least 500 µl of stored serum available for the study
3) For women, post-menopausal as of the time of the 1997 survey

[c] The sub-cohort was a random sample stratified by sex (500 men and 500 women). The sub-cohort sample size was based on consideration of study power (including for sex-specific analyses) and cost.

[d] After the sub-cohort was selected, it was determined that the available serum was insufficient for 1 person (female) selected for the sub-cohort.